PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/000340	15.01.2005	28.01.2004

International Patent Classification (IPC) or both national classification and IPC
C12Q1/37

Applicant
BAYER HEALTHCARE AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hennard, C Telephone No. +49 89 2399-7355

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000340

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000340

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-26(part)

because:

☒ the said international application, or the said claims Nos. 26 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-26(part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-26(part)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18, 24-26
	No:	Claims	19-23
Inventive step (IS)	Yes:	Claims	1-18, 24-26
	No:	Claims	19-23
Industrial applicability (IA)	Yes:	Claims	1-25
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. **Claim 26** relates to subject-matter considered by this Authority to be covered by the provisions of **Rule 67.1(iv) PCT** (method of treatment of humans related disease). Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (**Article 34(4)(a)(i) PCT**).

2. **Claims 19-21 and 24-26** involve an agent which binds/regulates KLK15 for which no structural indication is given in the claims besides the agent being an antisense oligonucleotide, an antibody or a ribozyme. Thus, these claims are unclear (**Article 6 PCT**) to what the agent can be and have been search only in relation to an agent being and antisense, an antibody or a ribozyme.

Re Item IV

Lack of unity of invention

1. Claims 1-26 (part)
   Method of screening for therapeutical agents useful in the treatment of cardiovascular diseases; method for diagnosing cardiovascular diseases; pharmaceutical compositions comprising agents which bind/regulate the activity of or comprising a KLK15 polypeptide for the treatment of cardiovascular diseases; pharmaceutical composition comprising a KLK15 polynucleotide for the treatment of cardiovascular diseases; method for the preparation of a pharmaceutical composition for the treatment of cardiovascular diseases.

2. Claims 1-26 (part)
   Method of screening for therapeutical agents useful in the treatment of cancer; method for diagnosing cancer; pharmaceutical compositions comprising agents which bind/regulate the activity of or comprising a KLK15 polypeptide for the treatment of cancer; pharmaceutical composition comprising a KLK15 polynucleotide; method for the preparation of a pharmaceutical composition for the treatment of cancer.

3. Claims 1-26 (part)
   Method of screening for therapeutical agents useful in the treatment of gastro-enterological diseases; method for diagnosing gastro-enterological diseases;

pharmaceutical compositions comprising agents which bind/regulate the activity of or comprising a KLK15 polypeptide for the treatment of gastro-enterological diseases; pharmaceutical composition comprising a KLK15 polynucleotide; method for the preparation of a pharmaceutical composition for the treatment of gastro-enterological diseases.

4. Claims 1-26 (part)
Method of screening for therapeutical agents useful in the treatment of inflammation; method for diagnosing inflammation; pharmaceutical compositions comprising agents which bind/regulate the activity of or comprising a KLK15 polypeptide for the treatment of inflammation; pharmaceutical composition comprising a KLK15 polynucleotide; method for the preparation of a pharmaceutical composition for the treatment of inflammation.

5. Claims 1-26 (part)
Method of screening for therapeutical agents useful in the treatment of metabolic diseases; method for diagnosing metabolic diseases; pharmaceutical compositions comprising agents which bind/regulate the activity of or comprising a KLK15 polypeptide for the treatment of metabolic diseases; pharmaceutical composition comprising a KLK15 polynucleotide for the treatment of metabolic diseases; method for the preparation of a pharmaceutical composition for the treatment of metabolic diseases.

6. Claims 1-26 (part)
Method of screening for therapeutical agents useful in the treatment of haematological diseases; method for diagnosing haematological diseases; pharmaceutical compositions comprising agents which bind/regulate the activity of or comprising a KLK15 polypeptide for the treatment of haematological diseases; pharmaceutical composition comprising a KLK15 polynucleotide for the treatment of haematological diseases; method for the preparation of a pharmaceutical composition for the treatment of haematological diseases.

7. Claims 1-26 (part)
Method of screening for therapeutical agents useful in the treatment of respiratory diseases; method for diagnosing respiratory diseases; pharmaceutical compositions comprising agents which bind/regulate the activity of or comprising a KLK15 polypeptide for the treatment of respiratory diseases; pharmaceutical composition

comprising a KLK15 polynucleotide for the treatment of respiratory diseases; method for the preparation of a pharmaceutical composition for the treatment of respiratory diseases.

8. Claims 1-26 (part)
Method of screening for therapeutical agents useful in the treatment of neurological diseases; method for diagnosing neurological diseases; pharmaceutical compositions comprising agents which bind/regulate the activity of or comprising a KLK15 polypeptide for the treatment of neurological diseases; pharmaceutical composition comprising a KLK15 polynucleotide for the treatment of neurological diseases; method for the preparation of a pharmaceutical composition for the treatment of neurological diseases.

9. Claims 1-26 (part)
Method of screening for therapeutical agents useful in the treatment of reproduction disorders; method for diagnosing reproduction disorders; pharmaceutical compositions comprising agents which bind/regulate the activity of or comprising a KLK15 polypeptide for the treatment of reproduction disorders; pharmaceutical composition comprising a KLK15 polynucleotide for the treatment of reproduction disorders; method for the preparation of a pharmaceutical composition for the treatment of reproduction disorders.

10. Claims 1-26 (part)
Method of screening for therapeutical agents useful in the treatment of urological diseases; method for diagnosing urological diseases; pharmaceutical compositions comprising agents which bind/regulate the activity of or comprising a KLK15 polypeptide for the treatment of urological diseases; pharmaceutical composition comprising a KLK15 polynucleotide for the treatment of urological diseases; method for the preparation of a pharmaceutical composition for the treatment of urological diseases.

The only concept which could possibly link the subject-matter of claims 1-26 of the present application, as required by **Rule 13.1 PCT**, could be seen in the association of kallikrein 15 with a disease. According to the description (pages 91-95) KLK15 is up-regulated in certain tissues and therefore, the applicant has inferred an association of KLK15 expression with certain diseases.

This concept is however known from the prior art (see **D1** Carsten et al; J. Urology, (2003), vol. 169, pages 361-364; page 363, "Discussion") which demonstrates that KLK15 is associated with more aggressive types of prostate cancer using RT-PCR. Moreover, WO 02/097438 (**D2**) on page 3, line 31 page 4, line 2 and claims 4 and 22 disclose methods for screening a subject for prostate cancer by detecting the amount of hK11 and KLK15 as a secondary marker for the cancer.

From these documents, it is concluded that the concept linking the above mentioned inventions is not new and cannot be seen as a common inventive concept. Therefore, the problem to be solved by the present application can be seen in the concept of providing methods for screening therapeutic agents useful in the treatment of different categories of diseases. The methods and pharmaceutical agents of the application constitute solution to different problems to be solved, each category of diseases corresponding to a different problem and the application as filed is considered to lack unity (**Rule 13.1 PCT**).

Further, the applicant is informed that in the light of the documents cited, further subdivisions of the inventions could be made. However, for the sake of efficiency, it has been renounced to proceed to these subdivisions. Nevertheless, an objection for lack of unity of the inventions is not excluded should the file proceed in the national/regional phase.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
   D1: JOURNAL OF UROLOGY, vol. 169, no. 1, January 2003 (2003-01), pages 361-364,
   D2: WO 02/097438 A
   D3: ENDOCRINE REVIEWS, vol. 22, no. 2, April 2001, pages 184-204,

   D4: WO 2004/029285 A
   D5: WO 02/14485-A

2. **Novelty (Article 33(2) PCT):**
   2.1 **D1** (page 362, left-hand column) describes the quantitative amplification of

KLK15 using RT-PCR. This document is thus considered to disclose a pharmaceutical composition comprising a KLK15 polynucleotide and is anticipating **claim 22** of the present application.

2.2 **D2** (page 3, line 20 - page 4, line 2; page 12, lines 9 - page 14, line 2; claims 4 and 22) disclose a method for screening a subject for prostate cancer involving as a second marker the KLK15 gene or to the KLK15 polypeptide. Thus **D2** discloses a composition containing an agent capable of binding with KLK15 polypeptide or KLK15 polynucleotide and is thus anticipating **claims 19-23** of the present application.

2.3 **D5** (page 21, paragraph 4.3; claims) discloses the use of KLK15 for the preparation of medicaments in the treatment of cancer. In the light of **D5**, **claims 19-23** are not novel.

2.4 In order to summarise, **claims 19-23** are not new and do not fulfil the requirements of Article 33(2) PCT whereas **claims 1-18 and 24-26** are novel.

3. **Inventive merit (Article 33(3) PCT):**

D3 (page 197, table 9 and part XI), which is the closest prior art, discloses the difference in expression level of KLK15 in specific tissues. The methods of the present independent **claims 1-3, 12, 18 and 24-26** are all characterised in that KLK15 is associated with cardiovascular diseases.

Since none of the prior discloses or suggests that KLK15 could be associated with cardiovascular diseases, and since from the table of page 91 of the description it is established that KLK15 is over expressed in tissues related with the heart (heart atrium, artery, coronary artery), the skilled person in charge of providing new agents susceptible to be used for the treatment of this diseases has no incentive to consider the use of KLK15 for the screening of such agents. It is thus concluded that **claims 1-3, 12, 18 and 24-26** fulfil the requirements of **Article 33(3) PCT**.

4. **Industrial applicability (Article 33(4) PCT):**

An industrial applicability of the invention is obvious and **claims 1-25** of the present application are considered to fulfil the requirements of **Article 33(4) PCT**.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/029285	08.04.2004	26.09.2003	26.09.2002

D4 which is an intermediate document, filed on 26.09.2003, published on 08.04.2004 and claiming a priority right on 26.09.2002, is not prior art according to the Chap II PCT proceedings and will not be used further at this stage (**Rule 70.10 PCT**). Nevertheless, the Applicant is informed that the content of this document seems to affect the novelty of the present application and could thus become relevant in the national/regional phase. Moreover, should the priority of the present application not be valid, **D4** could become also relevant for inventive step.

Re Item VII
Certain defects in the international application

1. Contrary to the requirements of **Rule 5.1(a)(ii) PCT**, the relevant background art disclosed in **D1** and **D2** is not mentioned in the description, nor are these documents identified therein.

2. Due to the high number of independent claims, the present application is considered not to fulfil the requirements of **Rule 6.1(a) PCT**.

Re Item VIII
Certain observations on the international application

1. For the assessment of the present **claim 26** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.